REMARKS

Claims 1-5, 7, 9-19, and 21-25 are pending in the application. Claims 1, 2, 10, 11, and 19 have been amended. Support for the amendments to claims 1 and 10 can be found in the specification, e.g., at page 8, first and fourth paragraphs, and at the last two lines on page 6. Applicants propose to amend claims 2 and 11 to delete the recitation of "highly expressing PTHrP," because that language is redundant in view of the amendments to claims 1 and 10, from which claims 2 and 11 depend, respectively. Claim 19 has been amended solely for purposes of clarity.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Action at page 2. Specifically, the Examiner alleged that

> the teaching of *Fodstad et al* and achievement in the art since are limited to immunodeficient nude rat and SCID mice, while claim recitation, "immunodeficient" is not limited to such, it encompasses any level or state (temporary or permanent) of an immunodeficient condition, whereas the establishment of a rodent bone metastasis model require profound immunocompromised state in rodent.

Action at pages 2-3. Applicants respectfully traverse.

Claim 1 has been amended to recite:

> A rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, in which a single cell suspension of tumor cells that induce bone metastasis and highly express PTHrP has been introduced by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal, wherein the animal is immunodeficient, and wherein the metastasis occurs in the animal's own bone.

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Claim 2, which depends from claim 1, has been amended to recite "[t]he rodent bone metastasis model animal according to claim 1, wherein the tumor cells are human lung cancer or breast cancer derived cells." Claims 3-5, 7, 9, 24, and 25 also ultimately depend from claim 1. Claim 10 has been amended to recite:

> A method for producing a rodent exhibiting bone metastasis of tumor cells, comprising:
>
> (i) providing an immunodeficient rodent; and
>
> (ii) introducing a single cell suspension of tumor cells that induce bone metastasis and highly express PTHrP into the animal by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal, wherein the metastasis occurs in the animal's own bone.

Claim 11, which depends from claim 10, has been amended to recite "[t]he method according to claim 10, wherein the tumor cells are human lung cancer- or breast cancer-derived cells." Claim 19, which depends from claim 10, has been amended to recite "[t]he method according to claim 10, wherein the single cell suspension of tumor cells is introduced by intravenous administration." Claims 10-18 and 21-23 also ultimately depend from claim 10.

First, applicants traverse the statement that "the establishment of a rodent bone metastasis model require[s] profound immunocompromised state in rodent." The Examiner provided no support for that statement, and it is unclear what is meant by "profound" and what level of immunocompromised state would be considered "profound." In contrast, however, one skilled in the art would understand the meaning of the term "immunodeficient," and would understand the claims to encompass many types of immunodeficient animals, including, but not limited to, nude rats, nude mice,

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irradiated mice, SCID mice, athymic mice, and the like. Such immunodeficient animals are discussed further below.

Second, applicants reiterate and incorporate by reference the arguments made in the Amendment and Response filed March 21, 2003, at pages 4 and 5 concerning the Fodstad article. Briefly, Fodstad was published seven years before the filing of the instant application. Fodstad indicates that "during the last decade an increasing number of investigators have reported on models for spontaneous and experimental human metastasis." Fodstad at page 23, right column. Thus, for at least 17 years prior to the filing date of the instant application, researchers have been successfully developing animal models for human tumor metastasis. Rather than question the level of skill in the art, Fodstad fully supports the applicants' contention that the level of skill in the art of human tumor metastasis model animals was high at the time of filing.

Furthermore, the achievements in the art since Fodstad have *not* been limited to the "immunodeficient nude rat and SCID mice." As support, applicants enclose several articles detailing metastasis models in immunodeficient animals other than nude rats and SCID mice. Those articles are cited in the Information Disclosure Statement and listed on the Form PTO 1449 filed herewith, and copies of those articles are enclosed.

For example, Turner et al., *J. Neuro-Oncol.*, 8: 121-132 (1990), discuss three types of immunodeficient mice: athymic nude mice, NK-deficient beige mice, and beige-nude mice, which are deficient in both T cells and NK cells. *See* Turner et al. at page 123, right column, under the heading "Murine hosts," to 124, left column. Faguet et al., *Blood*, 71: 422-429 (1988), discuss immunodeficient nude mice that have been preconditioned with total body irradiation. *See* Faguet et al. at page 423, right column,

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under the heading "Tumorigenicity studies." Jamasbi et al., *Br. J. Cancer*, 36: 723-729 (1977), discusses immunodeficient thymectomized, x-irradiated DBA/2 mice. *See* Jamasbi et al. at the abstract. Ishigaki et al., *Folia Microbiol.*, 43:493-494 (1998), discuss *xid/xid(nu/nu)* doubly immunodeficient mice and *xid/xid;bg/bg(nu/nu)* triply immunodeficient mice, in addition to *bg/bg(nu/nu)* doubly immunodeficient mice, which were discussed above. *See* Ishigake et al. at the abstract.

In sum, many types of immunodeficient model animals were known in the art at the time the application was filed. Thus, one skilled in the art would have been able to carry out the claimed invention using model animals other than simply the "immunodeficient nude rat and SCID mice" without undue experimentation, according to the teachings in the specification and the knowledge in the art at the time of filing.

The Examiner further alleged that the "claim recitation, 'tumor cells that induce bone metastasis' encompasses *any* and *all* tumors that are metastatic, and not even limited to human lung or breast tumors that may be determined by the levels of PTHrP." Applicants respectfully traverse. As shown in the specification, e.g., at page 14, Table 1, many metastatic tumors do not induce bone metastasis. Applicants therefore assert that the recitation "tumor cells that induce bone metastasis" does *not* encompass "any and all tumors that are metastatic." However, solely to expedite prosecution and without acquiescing to the rejection, applicants propose to amend claims 1 and 10 to recite "tumor cells that induce bone metastasis and highly express PTHrP." As discussed in the specification, e.g., at page 11, last paragraph, and at Example 5, cells that highly express PTHrP have the greatest potential to form bone mestastases. Moreover, the specification provides more than sufficient guidance by which one skilled

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in the art could determine whether tumor cells highly express PTHrP, e.g., at Example 5, and whether those cells form bone metastases, e.g., at Examples 1 and 2. Therefore, one skilled in the art would have been able to select a tumor cell line that highly expresses PTHrP and make a model animal according to claims 1 and 10 without undue experimentation at the time of filing. Dependent claims 2-5, 7, 9, 11-19, and 21-25 are also enabled for at least the reasons discussed above for claim 1 and 10.

Thus, the specification fully enables claims 1-5, 7, 9-19, and 21-25, and applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102

Applicants acknowledge the examiner's withdrawal of prior rejections based on Namikawa and on Miki et al.

The Examiner maintained the rejection of claims 1, 2, 4, 5, 10, 11, 24, and 25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Engebraaten et al., *Int. J. Cancer*, 82: 219-225 (1999) (hereafter "Engebraaten"). Action at page 5. Specifically, the Examiner alleged that "[t]he specification does not exclude the intracardial injection as peripheral administration."

Independent claims 1 and 10 and dependent claims 2 and 11 have been amended as discussed above. Claims 4, 5, 24, and 25 ultimately depend from claim 1. Claim 11 depends from claim 10.

Solely to expedite prosecution and without acquiescing to the rejection, Claims 1 and 10 have been amended to recite that the tumor cells are introduced "by at least one

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administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal." Applicants assert that Engebraaten does not teach a rodent bone metastasis model animal in which tumor cells are introduced "by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal," as recited in claim 1. Engebraaten also does not teach a method for producing a rodent exhibiting bone metastasis of tumor cells comprising introducing tumor cells "by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal," as recited in claim 10. Rather, Engebraaten only obtained bone metastases following direct intracardial injection of tumor cells..

The Examiner further alleged that "the tumor cells injected into the cardiac ventricle would flow into veins rapidly, as does using intravenous injection." Action at page 5. Applicants respectfully traverse. First, the Examiner cites no authority in support of the proposition that cells injected into the cardiac ventricle "would flow into veins rapidly." Moreover, in order to anticipate a claim, a reference must teach each and every limitation of that claim. As discussed above, Engebraaten does not teach *introducing* tumor cells "by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal." Thus, Engebraaten cannot anticipate independent claims 1 and 10. Claims 2, 4, 5, 11, 24, and 25 each ultimately depends from either claim 1 or claim 10 and therefore are also not anticipated by Engebraaten for at least the reasons discussed above for claims 1 and 10.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 4, 5, 10, 11, 24, and 25 under 35 U.S.C. § 102(b) over Engebraaten.

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The Examiner maintained the rejection of claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,365,797 (hereafter "Sawyers"). Action at page 5.

Independent claims 1 and 10 have been amended as discussed above. Claims 4, 5, 7, 9, 24, and 25 ultimately depend from claim 1. Claims 13-15 and 21-23 ultimately depend from claim 10.

First, the Examiner alleged that "[a]pplicants have not particularly pointed out where in the cited patent that Sawyers distinguishes the tissue from cell in tumor inoculation." Action at page 6. Applicants apologize for the omission. Sawyers distinguishes between implantation of tumor xenografts and injection of single cell suspensions of tumor cells, e.g., at Examples 1 through 8. For instance, in Example 1, Sawyers discusses implanting 2-3 mm^3 section of biopsy material into SCID mice (see, e.g., column 15, lines 35-40; see also Examples 3 and 7), while in Example 2, Sawyers discusses making single cell suspensions from biopsy tissue (see, e.g., column 22, lines 51-67; se also Examples 4-6 and 8). Thus, applicants reiterate their assertion that Sawyers distinguishes between the implantation of tumor tissue and the injection of tumor cells.

Second, the Examiner alleged that "the claims are not limited to administering cell suspension." Action at page 6. Solely to expedite prosecution and without acquiescing to the rejection, claims 1 and 10 have been amended to recite introduction of "a singe cell suspension of tumor cells that induce bone metastasis and highly express PTHrP."

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Third, the Examiner alleged that "Sawyers teaches both inoculating chunk tumor tissue and cell suspensions (See figure 5) by subcutaneous injection." Action at page 6. The Examiner further alleges that

> *Sawyers et al* clearly teach establishing a SCID mouse model for bone metastasis using human prostate cancer LAPC-4 cells by subcutaneous inoculation (e.g. column 23, lines 16-17), the mice subsequently developed consistent bone/bone marrow metastases in addition to lymph and pulmonary metastasis tumors, wherein an enhanced frequency of bone metastasis was observed in a subset of the mice pretreated with a combination of radiation and NK cell depletion (column 24, lines 31-35).

Id (emphasis in original).

Applicants respectfully traverse. The experiments cited by the Examiner actually involved implantation of LAPC-4 tumors, and not injection of LAPC-4 cells. Moreover, the mice implanted with those tumors failed to develop bone metastases. Specifically, Sawyers states in Example 3 that

> [t]he LAPC-4 xenograft was used in this study. This xenograft was derived from a lymph node containing metastatic prostate cancer cells, and 100% of male mice inoculated subcutaneously with LAPC-4 cells develop localized tumors after 4-6 weeks without evidence of bony [*sic*, bone] metastasis. The presence of micrometastasis in SCID mice implanted with LAPC-4 tumors was determined by analyzing the peripheral blood for prostate cancer cells using RT-PCR assays for PSA mRNA.

Sawyers at column 23, lines 14-22 (emphasis added). As Sawyers clearly states, the mice described in this example only developed bone micrometastases, and not bone metastases. Sawyers distinguishes micrometastases from metastases, e.g., at column 6, lines 49-51. Bone micrometastasis involves the mere presence of prostate tumor cells in bone marrow, without any visible bone lesions as would be characteristic of a bone metastasis. Thus, the Example cited by the Examiner shows implantation of

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tumor biopsy *tissue* that causes only bone *micrometastasis* in bone *marrow*, and not bone metastasis.

Furthermore, in the Examples involving inoculation of tumor cells into mice, Sawyers fails to demonstrate bone metastasis following injection of tumor cells "by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, or intraperitoneal," as recited in claims 1 and 10. Sawyers also fails to teach tumor cells that "highly express PTHrP," also as recited in claims 1 and 10. Thus, Sawyers fails to teach each and every element of claims 1 and 10 and therefore fails to anticipate those claims. Moreover, claims 4, 5, 7, 9, 13-15, and 21-25 each ultimately depend from either claim 1 or claim 10, and therefore are also not anticipated for at least the reasons discussed above for claims 1 and 10.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 under 35 U.S.C. § 102(e) over Sawyers.

Rejection Under 35 U.S.C. § 103 (a)

The Examiner maintained the rejection of claims 10 and 16-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sawyers in view of Yano. Action at page 7. Applicants respectfully traverse.

As discussed above, claim 10 has been amended to recite:

> [a] method for producing a rodent exhibiting bone metastasis of tumor cells, comprising:
>
> (i) providing an immunodeficient rodent; and
>
> (ii) introducing a single cell suspension of tumor cells that induce bone metastasis and highly express PTHrP into the animal by at least one administration route selected from intravenous,

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intramuscle, intracutaneous, subcutaneous, and intraperitoneal, wherein the metastasis occurs in the animal's own bone.

Claims 16-18 each depend from claim 10.

As discussed above, Sawyers fails to teach "[a] method for producing a rodent exhibiting bone metastasis," in which "tumor cells that induce bone metastasis and highly express PTHrP" are introduced "by at least one administration route selected from intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal," as recited by claim 10.

Because Sawyers fails as a primary reference, applicants need not and will not address the secondary reference, Yano, and this should not be construed as any acquiescence to those arguments. Moreover, since claims 16-18 ultimately depend from claim 10, for at least this reason, the Examiner has failed to establish that claims 16-18 would have been obvious over Sawyers in view of Yano.

For the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejection of claims 10 and 16-18 under 35 U.S.C. § 103(a) over Sawyers in view of Yano.

Applicants respectfully assert that claims 1-5, 7, 9-19, and 21-25 are in condition for allowance and request that the Examiner issue a timely Notice of Allowance. If the Examiner does not find the claims to be allowable, the undersigned requests that the Examiner call her at (650) 849-6656 to set up an interview.

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Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: December 1, 2003

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